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Electrospun nanofiber-based niflumic acid capsules with superior physicochemical properties

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ABSTRACT

The aim of this study was to assess whether nanofibrous drug mats have potential as delivery systems for poorly water-soluble drugs. Amorphous nanofiber mats from a model poorly water-soluble active pharmaceutical ingredient (API), niflumic acid, together with the polymer excipient, polyvinyl pyrrolidone, were prepared by nozzle-free electrospinning. This technique offers a scalable way for drug formulation, and by increasing the surface area of the drug, the dissolution rate and therefore bioavailability of the API can be improved. In this study, both the amount of the dissolved active ingredient and the dissolution kinetics has been improved significantly when the nanofibrous mats were used in the drug formulation. A 15-fold increase in the dissolved amount of the produced amorphous niflumic acid nanofiber was observed compared to the dissolved amount of the raw drug within the first 15 minutes. Capsule formulation was made by mixing the electrospun nanofibers with a microcrystalline cellulose filler agent. When comparing the dissolution rate of the capsule formulation on the market with the nanofibrous capsules, a 14-fold increase was observed in the dissolved drug amount within the first 15 minutes.

Keywords: *electrospinning, amorphous solid dispersion, poorly water-soluble drug, niflumic acid, physicochemical analysis*

1. INTRODUCTION

As the majority of the active pharmaceutical ingredients (APIs) in the pipeline are either insoluble or poorly soluble in water, solving bioavailability problems is crucial for the pharmaceutical industry [1–3]. One way to increase water solubility and/or dissolution rate is to produce the drug in nano-size range, as higher surface area leads to improved solubility and dissolution rate [4]. Another approach for increasing the bioavailability of crystalline drugs is to make the drug into an amorphous form [5].

Niflumic acid (NIF) is a widely used active pharmaceutical ingredient and is the structural analogue of anthranilic acid. NIF has anti-inflammatory activity accompanied by an analgesic effect [8]. It is primarily used to treat different forms of rheumatism and relieve other inflammatory states, the main side-effects being nausea or vomiting [9]. According to the Biopharmaceutics Classification System, NIF belongs to class II, a low water-soluble ($26 \mu\text{g mL}^{-1}$ at 25°C), lipophilic and highly permeable compound [10]. To achieve optimal pharmacodynamic properties such as a rapid onset of the drug effect, fast dissolution is important for this type of drug. Previous studies aimed to improve the solubility and dissolution rate of NIF by physical mixing, kneading [6], microwave irradiation [7] and electrospray crystallization [8,9]. These methods used PVP as a stabilizer, as this polymer can prevent the aggregation of the small drug particles and inhibits the crystallization of NIF [10]. Electrospray crystallization is an inexpensive method for the fabrication of submicron-sized NIF, however, it is challenging to scale it up to pilot scales. A similar electrohydrodynamic process, electrospinning, is capable of producing continuous nanofibers at large scales with low costs [11,12]. Electrospinning uses polymeric viscous solutions, from which nanofibers are drawn by high voltage.

In the present paper, nozzle-free electrospinning is investigated for the fabrication of NIF nanofibers in the presence of PVP in the solution. The produced nanofiber drug is then mixed with a filler agent to form capsules. This formulation of nanofiber-based capsules is a novel way of drug development. The effects of the procedure on the product morphology and size distribution were studied by scanning electron microscopy. The structure of the products was investigated using differential scanning calorimetry and X-ray powder diffraction. Wettability

and *in vitro* dissolution rate profiles of the different samples are presented and compared with each other and with the raw drug.

2. MATERIALS AND METHODS

2.1 Materials

Niflumic acid (NIF) (2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid) was purchased from Sigma-Aldrich. Polyvinylpyrrolidone (PVP, $M_w=1,300,000$) was purchased from Alfa Aesar. The solutions were prepared with 95 % ethanol and 99.8 % anhydrous dimethylformamide (DMF), both purchased from Merck. Pharmacopoeia grade microcrystalline cellulose (Vitalcel) with the volume-basis median diameter value (D50) of 58.2 μm was used as a filler agent for capsule formulation.

2.2 Methods

Preparation procedure

Nozzle-free electrospinning technique was employed to fabricate nanostructured NIF-PVP composites from their liquid clear solutions using different concentrations in a home-built setup. The experimental setup has been described in detail elsewhere [12].

The solution was prepared by dissolving NIF and PVP in 2 different ratios (1:1 and 2:1) in ethanol, then 10 vol% DMF was added to the solution to decrease the solution conductivity. The used concentration was 30 - 30 mg mL^{-1} for the 1:1 NIF-PVP, and 60 - 30 mg mL^{-1} for the 2:1 NIF-PVP mixture (Table 1). The solution, containing the dissolved NIF and PVP, was poured into a Teflon (PTFE) bath. A copper-wire coil electrode (with coil spacing = 5 mm and coil diameter = 23 mm) fixed to a metal shaft was rotated through the solution at 3 rpm (see Figure 1A). The electrospinning process was carried out at a voltage of +45 kV applied to the copper-wire coil electrode, and -5 kV potential applied to the collector electrode, creating the potential difference of 50 kV. The electrostatic forces produced by the high voltage increase the surface charge density of the polymeric solution, and a conically-shaped jet, known as the Taylor cone forms [13–15] (Figure 1B). When the applied high voltage is further increased, the accumulated charge density on the surface of the Taylor cone will generate repulsive electrostatic forces that overcome the surface tension of the polymer solution. The resulting jet that is dispensed from the tip of the Taylor cone experiences electrical instabilities by the

applied electric field which causes it to elongate and bend. Upon solidification, nanofibers are produced [16] on the collector mat [17].

The potential difference for the coil electrode was provided by a Spellman SL2000 +60 kV power supply. The collector electrode was a 50 mm long solid stainless-steel rod rotated at 500 rpm by a high torque DC motor. The collector electrode was biased to -5 kV by a -20 kV Glassman WX20N50.0YB2 power supply to increase the collection efficiency. Two different electrode-collector working distances (*WD*) were studied: 125 and 140 mm (Table 1). All the other process parameters were fixed. The NF1 and NF2 samples were prepared at 140 mm *WD*, while the *WD* for the NF3 was lowered to 125 mm. The fabrication was carried out at 22.4 °C and 54% relative humidity. The electrospun NIF mat was removed from the collector drum with the help of a carbon blade (see Supplementary Fig. 1). The physical mixtures, containing the raw NIF and PVP in the same amount as in the electrospinning experiment, was prepared as a reference by evaporating ethanol at room temperature (designated in the text as PM 1:1 and PM 2:1).

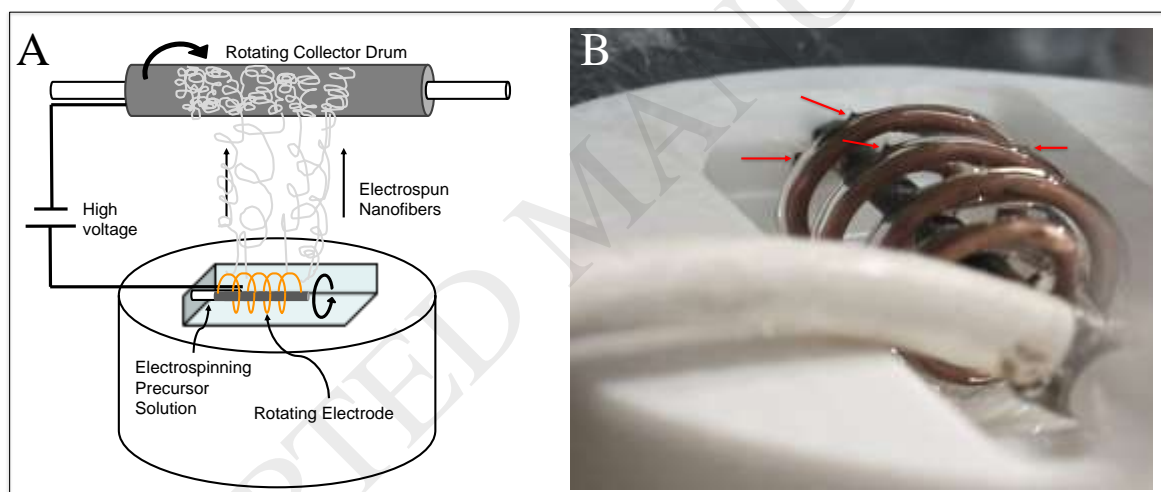


Fig. 1. **A.** Schematic drawing of the fabrication procedure by the nozzle-free electrospinning method. **B.** The rotating copper electrode immersed in the solution has a thin liquid film on its surface, from which the Taylor cones (highlighted by the arrows) emerge.

Sample composition

Two different sample compositions (1:1 and 2:1) were prepared in ethanol-DMF solutions (90% ethanol – 10 % DMF). The used concentration was 30-30 mg mL⁻¹ for the 1:1 NIF-PVP, and 60-30 mg mL⁻¹ for the 2:1 NIF-PVP.

Physical mixtures (PMs) in 1:1 (PM 1:1) and 2:1 (PM 2:1) ratios were prepared by a Turbula Mixer (T2F, Willy A. Bachofen AG, Muttentz, Switzerland), using the original or electrospun NIF with PVP (see Table 1).

Table 1. The composition of each sample and their preparation procedures.

Samples	NIF	PVP	Preparation procedure
NIF raw	1 g	-	Raw industrial form
PM 1:1	1 g	1 g	Mixing by Turbula mixer
PM 2:1	2 g	1 g	Mixing by Turbula mixer
NF1	60 mg mL ⁻¹	30 mg mL ⁻¹	Electrospinning, WD=140 mm
NF2	30 mg mL ⁻¹	30 mg mL ⁻¹	Electrospinning, WD=140 mm
NF3	30 mg mL ⁻¹	30 mg mL ⁻¹	Electrospinning, WD=125 mm

Capsule form was prepared using microcrystalline cellulose (VITACEL A300) as a filling agent. Microcrystalline cellulose promotes the homogeneous distribution of the API, which controls its dosing.

Microcrystalline cellulose was used to determine the space volume of the applied capsules (transparent, size 00 (23.3 mm locked length), Capsugel®, Switzerland). The maximum amount of powder mixture in the capsule was found to be 105 mg. In order to fill the capsule volume, 105 mg total mass of powder mixture was applied for each capsule. Care was taken to ensure that each capsule contained the same NIF dosage as the commercial drug (14 mg of NIF). The capsule containing the raw NIF was prepared by mixing 14 mg NIF with 91 mg microcrystalline cellulose (designated in the text as Caps-NIF), while the capsules containing the NIF nanofibers had reduced amount of cellulose, as they contained PVP in the nanofiber structure. The capsule prepared with the sample NF1 contained 14 mg NIF, 7 mg PVP and 84 mg Vitacel, while samples NF2 and NF3 contained 14 mg NIF, 14 mg PVP and 77 mg microcrystalline cellulose. In order to investigate the effect of the PVP on the solubility results, reference capsules were prepared by mixing the physical mixtures PM 1:1 and PM 2:1 with Vitacel (designated in the text as Caps-PM 1:1 and Caps-PM 2:1). The mixing was performed in a Turbula mixer for each sample, which was operated for 10 min at 50 rpm (Figure 2). Since the amount of nanofibers in the mixtures is significantly lower than the amount of the microcrystalline cellulose, it can be assumed that the presence of the fibers will not alter the flowability properties of the cellulose filler agent.

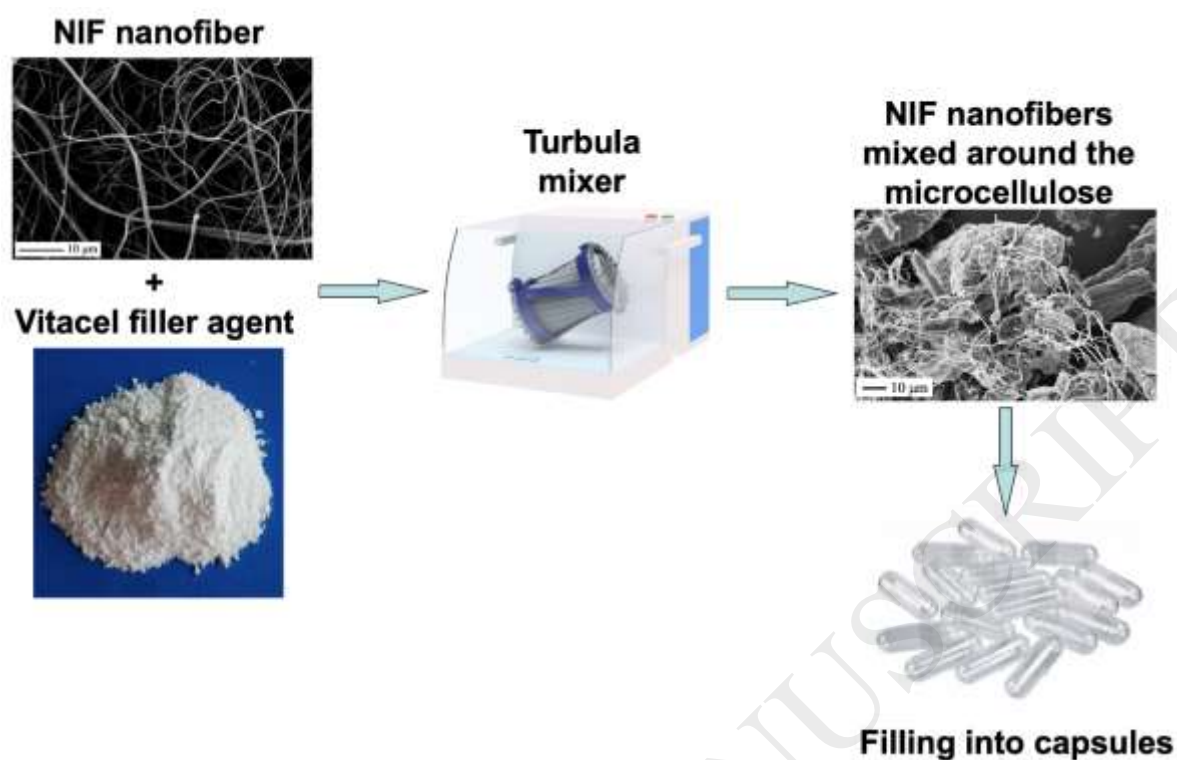


Fig. 2. Schematic illustration showing the formulation of the solid dosage form. NIF nanofibers were mixed with the microcrystalline cellulose filler agent (Vitacel) in a Turbula mixer. Then the mixtures were filled into capsules.

Table 2. The composition of NIF-contained capsules prepared by physical mixing and electrospinning.

Samples	Compositions
Caps-NIF	NIF-VITACEL A300
Caps-PM 1:1	PM 1:1- VITACEL A300
Caps-PM 2:1	PM 2:1- VITACEL A300
Caps-NF1	NF1- VITACEL A300
Caps-NF2	NF2- VITACEL A300
Caps-NF3	NF3 VITACEL A300

2.3. Analysis

Scanning electron microscopy

The morphology and size were analyzed using Scanning electron microscopy (SEM), by a Hitachi S4700 instrument (Hitachi Scientific Ltd., Tokyo, Japan) at 10 kV. The samples were gold-palladium coated (90 seconds) by a sputter coater (Bio-Rad SC 502, VG Microtech, Uckfield, UK) using an electric potential of 2 kV at 10 mA for 10 minutes. Image processing was done in the ImageJ software environment [18]. Over 150 individual particle measurements were made in at least five different images in order to determine the diameters of the nanofibers accurately.

Differential scanning calorimetry (DSC)

DSC was employed to investigate the crystallization behavior and the melting behavior of the conventional and submicron-sized NIF. The DSC measurements were made with a Mettler Toledo DSC 821^e thermal analysis system with the STAR^e thermal analysis program V9.1 (Mettler Inc., Schwerzenbach, Switzerland). Approximately 2 - 5 mg of the product was examined in the temperature range between 25 °C and 300 °C. The heating rate was 5 °C min⁻¹. Argon was used as a carrier gas, at a flow rate of 10 L h⁻¹ during the DSC investigation.

X-ray powder diffraction (XRPD)

XRPD was carried out to determine the crystalline form and crystallinity of the produced materials. Samples were analyzed by a Bruker D2 diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). Data collection was carried out at room temperature using monochromatic Cu K α 1 radiation ($\lambda = 0.154060$ nm) in the 2-theta region between 3° and 50°. The samples were placed on a zero-background holder (Si single crystal <510> wafer).

Solubility test

The solubility of NIF was determined in distilled water (pH 5.6) and at simulated gastric media buffer solution (pH 1.2) at 25 °C. 10 mg of the sample was placed into 5 mL of distilled water or buffer solution, and stirred with magnetic stirrer rigorously for 24 hours. Then the samples were filtered by a filter paper (0.22 μ m, FilterBio PES Syringe Filter, Labex Ltd., Budapest, Hungary) to remove any undissolved particles or impurities, and the content of dissolved drug in the liquid was measured spectrophotometrically at 256 nm (Unicam UV/Vis spectrophotometer, Germany).

Wettability studies

Optical contact angle measurement and drop contour analysis were performed using an OCA 20 system (Dataphysics Inc., GmbH, Germany) for measuring the wettability of the capsule products containing NIF. A small amount of powder (150 mg) was compressed under a pressure of 1 ton by a Specac hydraulic press (Specac Inc., USA). The wetting angles of the pressings were determined after 4.3 μL of distilled water had been dropped onto the surface of the pressed samples. The change in the wetting angle was registered from 1 to 25 s, using the circle fitting method of the OCA system. The method of Wu was applied, in which two liquids with known polar (γ_l^p) and dispersion (γ_l^d) components are used for measurement [19]. The solid surface free energy is the sum of the polar (γ_s^p) and non-polar (γ_s^d) components and is calculated according to equation 1:

$$(1 + \cos\Theta)\gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \quad (1)$$

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension. The percentage of the polarity can be calculated from the γ^p and γ values: $(\gamma^p / \gamma) \times 100$. The liquids used for our contact angle measurements were double-distilled water ($\gamma^p = 50.2 \text{ mN m}^{-1}$, $\gamma^d = 22.6 \text{ mN m}^{-1}$) and diiodomethane ($\gamma^p = 1.8 \text{ mN m}^{-1}$, $\gamma^d = 49 \text{ mN m}^{-1}$). The results of the contact angle measurements using diiodomethane as non-polar component and water as polar component provide information on the surface free energies and polarities of the samples.

In vitro dissolution of nanofibers and formulated capsule products

The dissolution profile of product samples containing equal amounts of drug (14 mg of NIF according to its therapeutic dosage) was determined using the modified paddle method. A buffer solution (50 mL, pH 1.2 ± 0.1) at 37 ± 0.5 °C was used as a dissolution medium (simulated gastric medium) and the rotation speed of the paddles was 100 rpm. At certain time intervals, 2 mL solution samples were withdrawn and filtered (cut-off 0.2 μm , Minisart SRP 25, Sartorius, Germany) and the amount of dissolved drug was determined spectrophotometrically by an ATI-Unicam UV2-100 UV/VIS spectrophotometer at 256 nm. The amount of the withdrawn samples was replaced with fresh medium.

3. RESULTS AND DISCUSSION

3.1 Characterization of nanofibers containing NIF and PVP

Large nanofiber mats of NIF-PVP composites were produced using the nozzle-free electrospinning technique. This method is capable of producing high yields without any clogging problems, as the fibers are formed from a free surface. In our experiments, a 6×7.5 cm mat, with the weight of 100 mg was produced in just 10 minutes (see Supplementary Figure 1).

3.1.1 Micrometric properties

SEM study revealed that the size range of the nanofibers varied between 160 - 1800 nm, depending on the solution concentration parameters. The samples prepared from 1:1 NIF – PVP ratio solution have significantly smaller fiber diameters than the sample prepared from the 2:1 NIF – PVP ratio solution (see Figure 3 and Table 3).

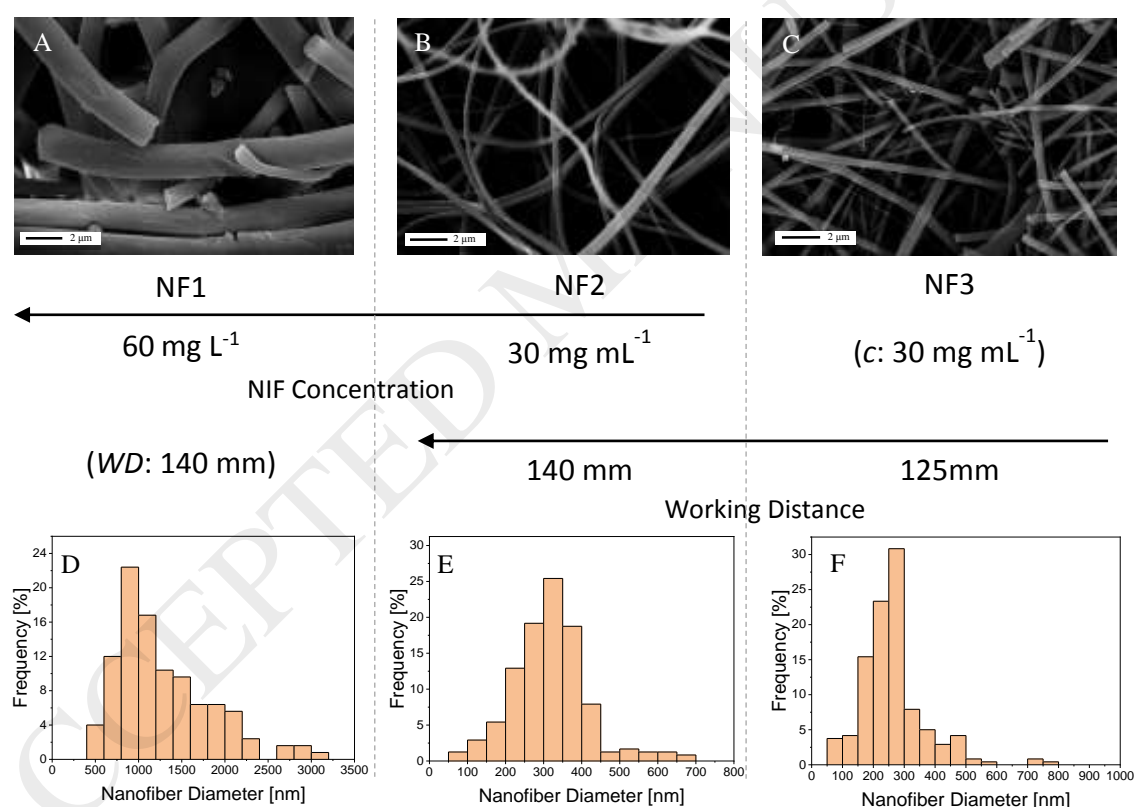


Fig. 3. SEM pictures (A-C) of the three nanofibers prepared and their respective nanofiber diameter distribution histograms (D-F). Their respective niflumic acid concentrations (c) and working distance (WD) are displayed on the axis between the graphs and pictures.

Analysis of the SEM images concluded that by optimizing the electrospinning process parameters, it is possible to reach NIF fibers with a mean diameter of 265 nm (see Table 3).

The average size of the manufacturer NIF was around 16 μm , and when adding the polymer, PVP, into the physical mixtures, the average size of the agglomerate can reach 24 - 27 μm . The electrospun samples were stored at room temperature (25 $^{\circ}\text{C}$) in a desiccator for 1 year, then their morphology and size were investigated again by SEM. The analysis showed no observable difference in their nanostructure when compared with the fresh samples (see Supplementary Fig. 2).

Table 3. The mean particle size (over volume) and mean diameter of the fibers with the Standard Deviation (SD) for the measured size distribution.

Samples	Mean particle size and SD [μm]	Mean fiber diameter and SD [nm]
Raw NIF	15.82 ± 2.43	-
PM 1:1	27.37 ± 0.98	-
PM 2:1	24.47 ± 1.54	-
NF1	-	1287 ± 551
NF2	-	317 ± 101
NF3	-	265 ± 104

3. 1. 2 Structural characterization

DSC was employed to investigate the melting points and crystallinity of NIF before and after the crystallization process. Single sharp endothermic peaks were observed (see Supplementary Fig. 3), corresponding to the melting points of the raw NIF (203.25 $^{\circ}\text{C}$). Because of the presence of the PVP, there is a physical interaction between NIF and excipient by heating. It has been previously found that NIF can be dissolved in the melted PVP, resulting in no melting point detected by DSC [20,21]. The TG analysis found no traces of organic solvents, and showed that the prepared samples were thermally stable compared to the raw NIF (Figure 4).

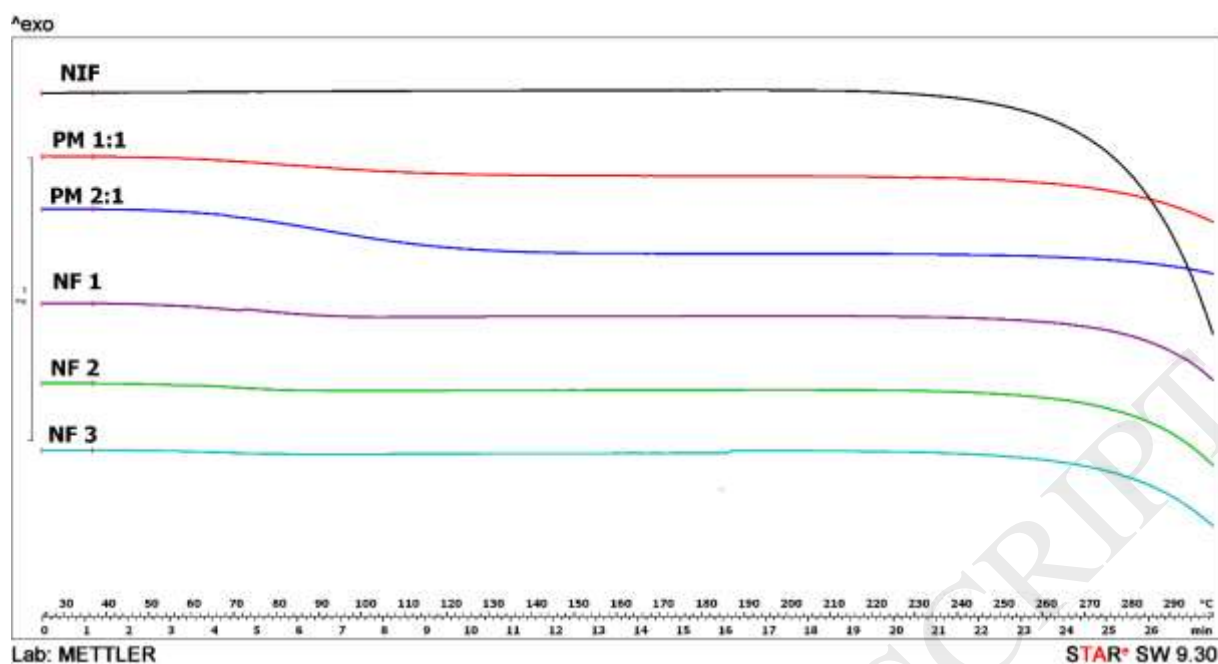


Fig. 4. The TG analysis of the samples showed no traces of organic solvents. The electrospun samples and the physical mixtures with PVP are thermally more stable than the raw NIF.

XRPD was used to examine the crystalline phase of the products. The characteristic peaks of NIF are the 2θ values of 8.2° , 12.88° , 16.16° , 23.18° and 25.4° . Both PMs show the characteristic peaks of NIF, however, all the electrospun nanofibers were amorphous (Figure 5). The XRPD measurement was repeated 1 year after the fabrication procedure, and the results were unchanged.

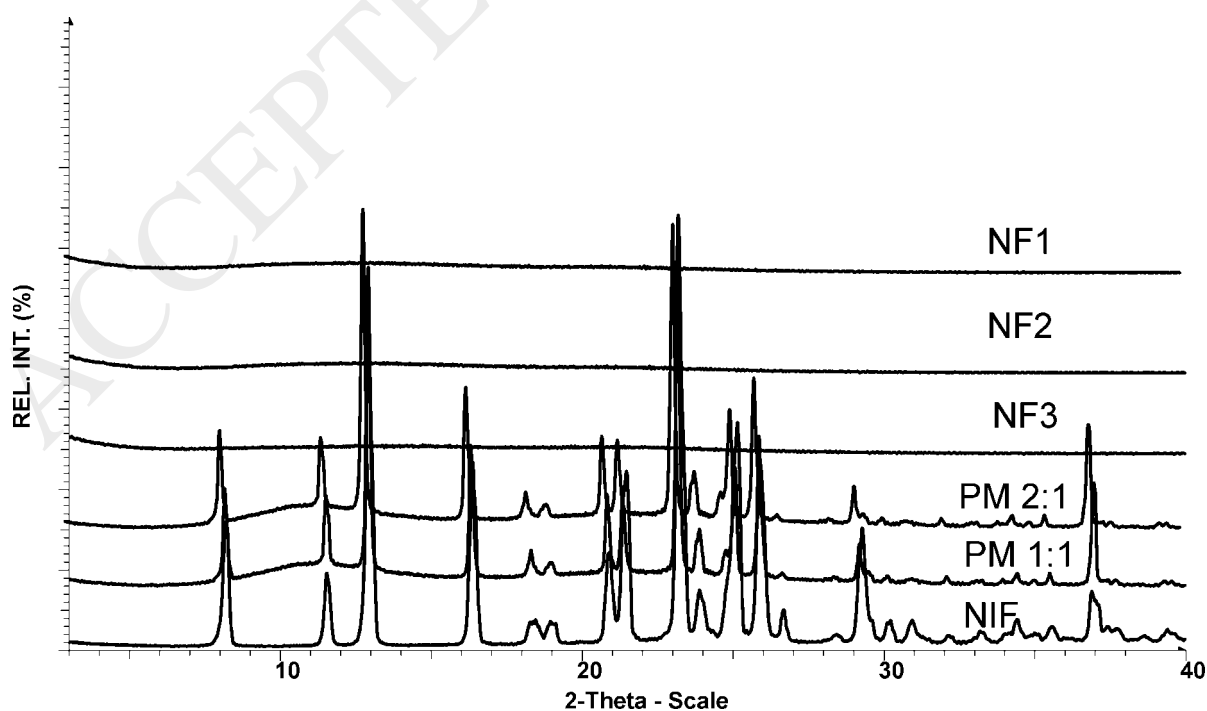


Fig. 5. XRPD pattern of the NIF, physical mixtures and NF samples. All the electrospun nanofiber samples were amorphous, while the physical mixtures were in a crystalline state.

3.1.3 Solubility test

NIF has an acidic character, and its solubility was, therefore, higher at pH 1.2 than at pH 5.5. The size reduction and presence of PVP, as a wetting agent (Table 4) caused an increase in solubility, especially on the NF3 sample. The PVP prepared by physical mixing resulted in a slight improvement in solubility. However, the electrospun nanofibers with the smallest diameter resulted in a significant, 3-fold increase of solubility in water, and up to 6-fold increase at acidic pH (see Table 4).

Table 4. The solubility data of the produced samples in phosphate buffer at pH 5.5 and gastric media at pH 1.2.

Samples	Solubility [mg mL ⁻¹] in water (pH 5.5)	Solubility [mg mL ⁻¹] in gastric media (pH 1.2)
NIF raw	0.026	0.24
PM 1:1	0.035	0.41
PM 2:1	0.029	0.37
NF1	0.081	0.55
NF2	0.043	0.52
NF3	0.055	1.57

3.1.4 Dissolution studies

When the two PMs (where no nanofibers were present) were measured in simulated gastric media (pH 1.2), the dissolution kinetics of NIF was slow, comparable to the raw NIF sample's dissolution speed. After 120 minutes, only 20% of the drug was liberated. The dissolution rate and dissolved concentration were significantly higher when the amorphous nanofibrous formulations were tested. Both NF1 and NF2 samples demonstrated ~74% dissolved NIF after 15 minutes. The sample, NF3, showed the fastest and highest dissolution behavior, just after 15 minutes, 97% of the drug has been dissolved into the simulated gastric fluid. This means a 5-fold increase in the amount of the dissolved API when compared with the conventional capsule

form in the first 120 minutes (Figure 6). Therefore, our results show that the dissolution behavior can be significantly improved by a nanofabrication method.

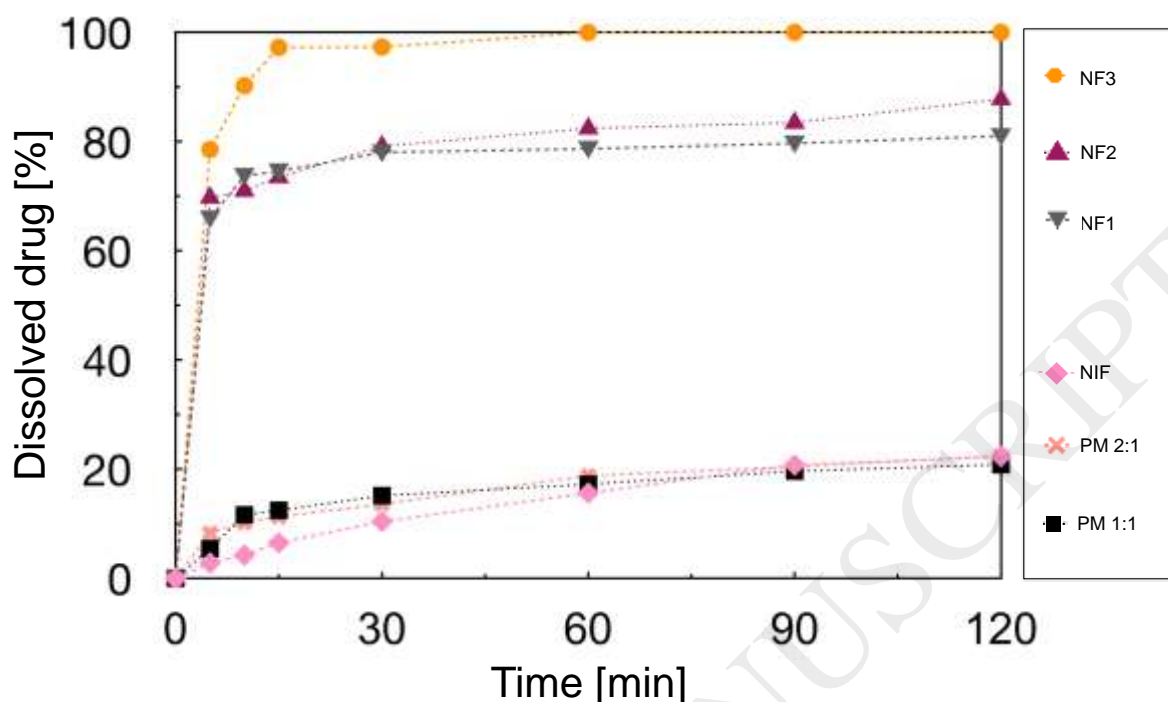


Fig. 6. In vitro dissolution of NIF from the nanofiber measured at pH 1.2. The nanofiber-based samples have improved dissolution kinetics, and significantly higher dissolution rates than the raw NIF or the physical mixtures (PMs).

3.2 Investigation of capsule form containing nanofibers

In general, the produced drug nanofibers could be easily used as dermal formulation (e.g. skin patches). The novelty of this work is the formulation of the solid dosage form capsules, which is significant, as NIF is applied generally in a capsule form [22]. Thus, capsules were also formulated, containing the NIF/PVP nanofiber mixtures and the cellulose filler.

3.2.1 Morphology of the powder mixtures containing nanofibers

During the mixing of the filler agent and nanofiber samples, the uniformity was different. In the case of electrospun fiber (NF3) and capsule formulation (CAPS-NF3) samples (Figure 7), a well-distributed mixture was reached, which can offer improved surface area (see Figure 7C).

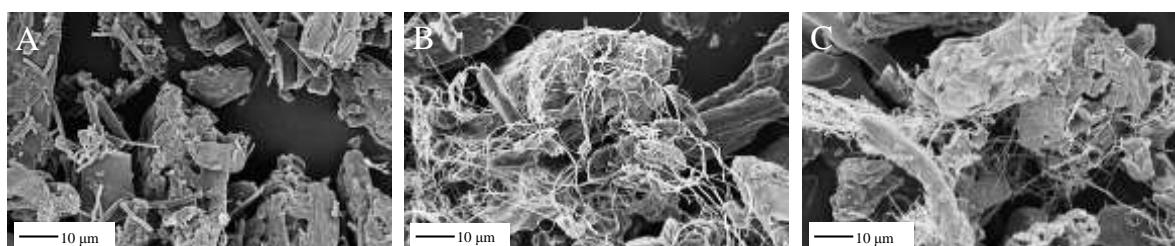


Fig. 7. SEM images showing the distribution of nanofibers around the filling agent (A. Caps-NF1, B. Caps-NF2 and C. Caps-NF3).

3.2.2 Wettability and dissolution profiles of the powder mixture in the capsule form

The wettability study indicates that the products containing the PVP, Vitacel and nanometer-size range of the drug have a hydrophilic character. Table 5 shows that relatively low contact angles with water were measured for these samples. The contact angle for the manufacturer NIF ($\sim 72^\circ$) was relatively high, revealing its hydrophobicity. The amorphous nature and the PVP covering a large surface of the NIF particles can be the reasons behind the increased wettability of the electrospun samples. PVP is known to have a surface tension lowering effect, resulting in wetting of the hydrophobic NIF crystalline surface [7,23,24]. The increased specific surface area and the amorphous character can also increase the wettability.

Table 5. Wettability results for the different samples.

Samples	θ_{water} [°]	$\theta_{\text{diiodomethane}}$ [°]	γ [mN m ⁻¹]	Polarity [%]
NIF	72.5	31.38	51.11	21.91
Caps-NIF	27.80	13.95	75.89	41.34
Caps-PM1	12.5	19.35	79.71	45.76
Caps-PM2	14.76	16.13	79.72	44.79
Caps-NF1	10.5	31.85	77.59	49.49
Caps-NF2	17.26	29.87	76.47	47.79
Caps-NF3	11.09	26.15	78.70	47.65

The hydrophilic character of the samples prepared with electrospun fibers results in a significantly improved dissolution behavior of the active ingredient, NIF. The dissolution results of the nanofiber-based capsules show outstanding kinetics, when compared to the capsules made with the PMs (Figure 8). The standard deviation of NIF concentration (measured

by UV/Vis spectrophotometry) was below 10%. When the two capsules with no nanofibers present (Caps-PM1 and Caps-PM2) were measured in simulated gastric media (pH 1.2), the dissolution kinetics of NIF was comparable to the raw NIF sample's slow dissolution speed, and slightly less drug dissolved out from these samples, when compared with the pure NIF sample's behavior. After 120 minutes, only ~20% of the drug was dissolved into the gastric fluid. The dissolution rate and dissolved concentration were significantly higher when the capsule formulations with nanofibers were tested. Both Caps-NF1 and Caps-NF2 samples demonstrated ~69% dissolved NIF after 15 minutes. The sample, Caps-NF3, showed the fastest and highest dissolution behavior, just after 15 minutes, 91% of the drug has been dissolved into the simulated gastric fluid. This means a 23-fold increase in the amount of the dissolved NIF, when compared with the conventional capsule form in the first 15 minutes, and a 5-fold increase is observed when compared with the conventional capsule form in the first 120 minutes.

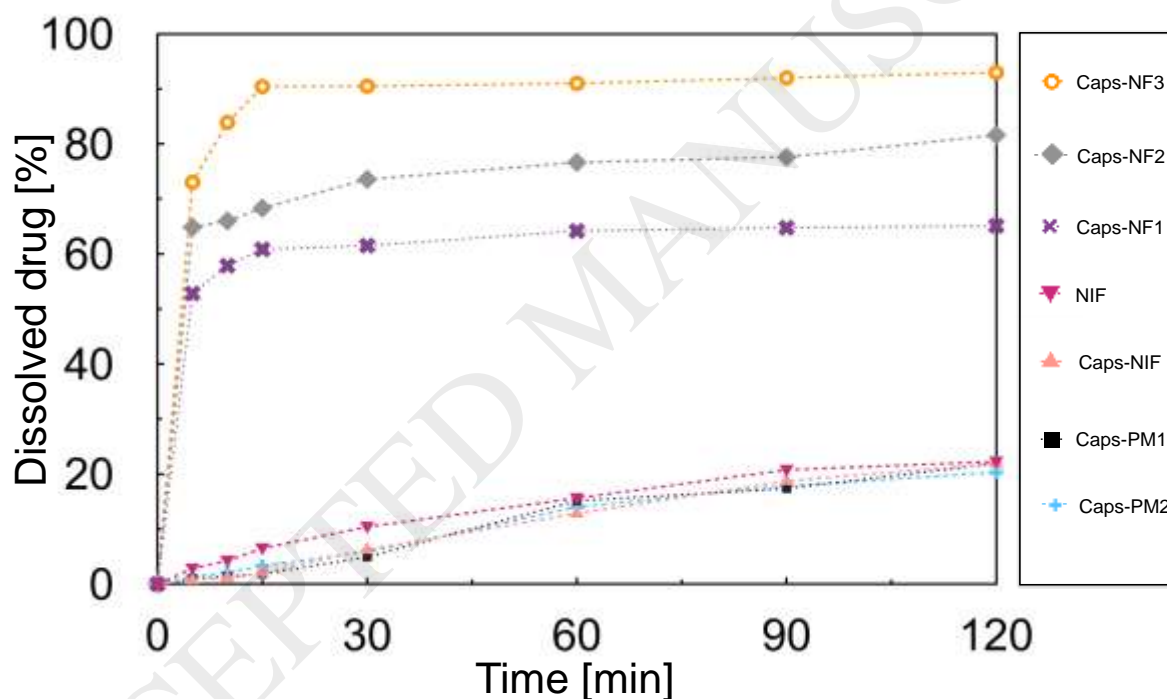


Fig. 8. In vitro dissolution behavior of the prepared capsules measured at pH 1.2. The nanofiber-based capsules show outstanding dissolution kinetics, when compared to the capsules made with the physical mixtures (PMs).

4. CONCLUSIONS

This study has shown that electrospinning is an effective method to change the physicochemical properties of the pharmaceutical active ingredient, NIF. It can be concluded that decreased size of the drug compound in the nano-size range can be achieved with this procedure, resulting in

a possibility of capsule formulation with nearly 100 % drug release. According to the structural analysis, the drug was in crystalline form when formulated without the PVP excipient, and in an amorphous form when prepared with PVP. The wettability and dissolution tests revealed the hydrophilic character of NIF produced by electrospinning, while the manufacturer NIF is hydrophobic. Nanofiber formulation of NIF using our method could reduce the gastric irritation of NIF and could facilitate its safe use. A 15-fold increase in the dissolution rate of the produced amorphous niflumic acid nanofiber mats was observed compared to the dissolution rate of the original drug within the first 15 minutes. When the dissolution rate of the original capsule formulation was compared with the nanofibrous capsules, a 23-fold increase was observed in the dissolution kinetics within the first 15 minutes. We conclude that during the pre-formulation and then the final formulation from the lipophilic NIF, we could form a capsule product with good stability due to its amorphous form, and nearly 100 % drug release in the gastric media. It means that the bioavailability may have been improved, therefore the dosage and unwanted side-effects could be decreased. Therefore, our results show that the dissolution behavior of poorly water-soluble drugs can be significantly improved by utilizing the electrospinning nanofabrication method.

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